SYNTHESIS OF 12-SUBSTITUTED ALKYL-8-CHLORO-6-PHENYL-11H-DIBENZO[b,g] [1,3,6] TRIAZONINES AS POSSIBLE ANTICONVULSANTS

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ABSTRACT

Eleven new 12-substituted alkyl-8-chloro-6-phenyl-11H-dibenzo[b,g] [1,3,6]triazonines were synthesized and screened for their acute toxicity, gross behavioural effects and anticonvulsant activity (metrazole and electroshock induced seizure test) in mice. Compounds with 12-aminomethyl substitution was 40% active against metrazole induced seizures while the other compounds could not exhibit any protection against metrazole or electroshock induced seizures.

INTRODUCTION

FLUPERLAPINE[1], MK-801[2], Amytriptyline[3] and Doxepin[3] have been used clinically as anticonvulsant, anxiolytic, neuroleptic and antidepressant. These CNS active drugs contain a dibenzoheterocyclic system as their fundamental structural feature. These observations have prompted the present authors to undertake the synthesis and anticonvulsant screening of some dibenzotriazonines (figure 1). Since the role of amide linkage[4–7], aminomethyl group[8,9] and 3,4,5-trimethoxyphenyl ring[10–12] for anticonvulsant activity is well understood and as these groups also increased the lipid solubility[13], it was considered worthwhile to incorporate these groupings at position 12 of the heterocyclic system and to study their effect on the biological activity.

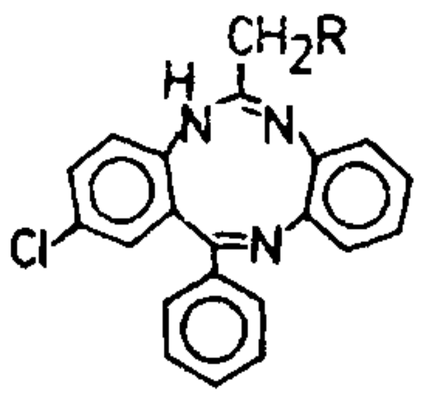

Figure 1.

EXPERIMENTAL PROCEDURE

The melting points were determined in open capillaries in sulphuric acid bath and were uncorrected. IR spectra were recorded on infracord spectrophotometer (Perkin-Elmer 157) using KBr discs. PMR spectra were recorded on spectrometer (Varian A60D) (60 MHz) using TMS as internal reference.

The reactions were followed on silica gel TLC plates and the spots were located by iodine vapours. All new compounds gave satisfactory C, H and N elemental analysis (table 1).

(i) *2-Amino-5-chlorobenzophenone* It was prepared according to the known procedure[14].

(ii) *2-Amino-5-chlorobenzophenone-o-aminoanil*: A mixture of 2-amino-5-chlorobenzophenone (0.926 g; 0.004 mol), *o*-phenylenediamine (0.864 g; 0.008 mol) and anhydrous sodium acetate (0.656 g; 0.008 mol) was refluxed in acetic acid (25 ml) for 70 hr. The reaction mixture was cooled diluted with cold water (200 ml) and left overnight. The separated crude product was filtered, dried and recrystallized from aqueous ethanol to give the product in 90–95% yield (1.15 g–1.22 g).
m.p.: 109–10°C.
IR (KBr): ν_{max}: ~3300 cm^{-1} (Primary amine), 1645 cm^{-1} (−C=N) and 1605 cm^{-1} (aromatic).

(iii) *12-Aminomethyl/chloromethyl-8-chloro-6-phenyl-11H-dibenzo[b,g] [1,3,6]triazonines (I and II; table 1)*
A mixture of phosphorous pentoxide (2 g) and *ortho* phosphoric acid (4 ml) was heated on a water bath for 4 hr. To this freshly prepared polyphosphoric acid (PPA) were added 2-amino-5-chlorobenzophenone-*o*-aminoanil (0.3215 g; 0.001 mol) and appropriate aliphatic acid (0.002 mol). The mixture was heated on a water bath for 12 hr. The reaction mixture was cooled to room temperature and treated with sodium bicarbonate solution (200 ml; 10%) with stirring. The separated solid was filtered, dried and recrystallised

from methanol to give the product in yields ranging between 60 and 90%.
IR (KBr): ν_{max}: ~3400 cm^{-1} (Primary and secondary amine), 1645 cm^{-1} (−C=N) and 1590 cm^{-1} (aromatic). ^1H nmr ($CDCl_3$) of II: δ: 1.35 (bs, 2H, NH_2), 2.2 (m, 2H, CH_2), 7.7–6.5 (m, 13H, ArH + NH).

(iv) 12-*Acetamidomethyl*-8-*chloro*-6-*phenyl*-11*H*-*dibenzo*[*b*,*g*][1,3,6]*triazonine* (*III*; *table* 1) 12-Aminomethyl-8-chloro-6-phenyl-11H-dibenzo[b,g][1,3,6] triazonine (II, 0.3605 g; 0.001 mol) was refluxed in acetic anhydride (5 ml) for 45 hr. The reaction mixture was cooled and poured on crushed ice and left overnight. The separated crude product was filtered, dried and recrystallised from methanol in 50–60% yields (0.20–0.24 g).
IR (KBr): ν_{max}: ~3300 cm^{-1} (NH), 1740 cm^{-1} (carbonyl amide), 1680 cm^{-1} (−C=N) and 1600 cm^{-1} (aromatic).

(v) 12-*Substituted amidomethyl/aminomethyl*-8-*chloro*-6-*phenyl*-11*H*-*dibenzo*[*b*,*g*] [1,3,6]*triazonines* (*IV–XI*; *table* 1) A mixture of 12-substituted methyl-8-chloro-6-phenyl-11H-dibenzo [b,g] [1,3,6]triazonine (I/II; 0.001 mol) and appropriate aroyl chloride (0.002 mol) or appropriate secondary amine (0.001 mol) and triethylamine (0.202 g; 0.280 ml, 0.002 mol) in dry benzene was refluxed for 15–20 hr. Triethylamine hydrochloride which separated out was filtered. The residue was recrystallized from methanol in yields 60–70%.
IR (KBr): ν_{max}: ~3300 cm^{-1} (NH), 2950 cm^{-1} (aliphatic CH in VII to XI), 1710 cm^{-1} (amide carbonyl in IV to VI), 1640 cm^{-1} (−C=N) and 1600 cm^{-1} (aromatic).

Bio-Assay

Albino mice of either sex, weighing between 16–20 g and fasted overnight were used. Aqueous suspension of compounds were prepared in gum acacia. Gross behavioural effects and anticonvulsant activity were observed at 1/5th of the LD_{50}. The results have been summarized in table 1.

Table 1 12-*Substituted methyl/amidomethyl/aminomethyl*-8-*chloro*-6-*phenyl*-11*H*-*dibenzo* [*b*,*g*][1,3,6]*triazonines* (*figure* 1)

Sl. No.	R	Molecular formula	m.p. °C	LD_{50} mg/kg i.p. (confidence limit)	Found(Calcd.) % C	H	N
I	chloro	$C_{21}H_{15}Cl_2N_3$	105	> 1000	66.23 (66.31)	3.79 (3.94)	10.77 (11.05)
II	amino	$C_{21}H_{17}ClN_4$	102–05	> 1000	69.81 (69.90)	4.63 (4.71)	15.28 (15.53)
III	acetamido	$C_{23}H_{19}ClN_4O$	93–95	1000 (6421560)	68.49 (68.57)	4.61 (4.72)	13.68 (13.91)
IV	benzamido	$C_{28}H_{21}ClN_4O$	155	681 (nil)	72.23 (72.33)	4.47 (4.52)	11.79 (12.05)
V	4-methoxybenzamido	$C_{29}H_{23}ClN_4O_2$	130	> 1000	70.31 (70.37)	4.53 (4.65)	11.02 (11.32)
VI	3,4,5-trimethoxy-benzamido	$C_{31}H_{27}ClN_4O_4$	135–40	1000 (642–1560)	68.89 (67.08)	4.72 (4.86)	9.84 (10.09)
VII	morpholino	$C_{25}H_{23}ClN_4O$	132–35	> 1000	69.56 (69.68)	5.27 (5.34)	12.72 (13.00)
VIII	diethanolamino	$C_{25}H_{25}ClN_4O_2$	140–43	> 1000	66.73 (66.88)	5.42 (5.57)	12.16 (12.48)
IX	N-phenylpiperazino	$C_{31}H_{28}ClN_5$	163–65	> 1000	73.48 (73.59)	5.41 (5.53)	13.58 (13.84)
X	N-methylpiperazino	$C_{26}H_{26}ClN_5$	155–57	> 1000	70.14 (70.34)	5.71 (5.86)	15.46 (15.78)
XI	dimethylamino	$C_{23}H_{21}ClN_4$	140	> 1000	70.93 (71.04)	5.27 (5.40)	14.14 (14.41)

At 1/5th of the LD_{50}, compounds exhibited no effect on the gross behaviour and II was 40% active against metrazole induced seizures. Other compounds were devoid of anticonvulsant activity against metrazole or electroshock-induced seizures.

Acute Toxicity Studies

The LD_{50} was determined in groups of 4 mice at each dose level using the method of Horn[15]. An initial dose of 464 mg/kg of compounds was administered i.p. The doses of compounds were increased or reduced depending on the mortality with the initial dose. Mortality at 4 such points was recorded and the table used to read the LD_{50} and confidence limits.

Gross Behavioural Effects

The method of Turner[16] was used. Different doses of compounds including 1/5th of the LD_{50} were administered i.p. in groups of 4–5 mice each. The animals were then observed for 6 hr and then at 24 hr for any sign of stimulation, depression and autonomic effects.

Anticonvulsant Activity

Metrazole Seizure Threshold Test: The procedure of Swinyard *et al*[17] was followed. Groups of 5 mice each, pretreated with the compounds i.p., were administered metrazole (80 mg/kg) subcutaneously after 1 hr. The animals were observed continuously for 1 hr for the appearance of clonic convulsions. The number of animals not exhibiting clonic convulsions were expressed in terms of percentage protection. Clonic convulsions of less than 5 sec duration were disregarded.

Supramaximal Electroshock Seizure Test: The method of Swinyard *et al*[17] was followed. Groups of 5 mice each were pretreated with the compound 1 hr earlier. A current stimulus of 48 mA for 0.2 sec delivered through ear electrodes produced tonic extension of hind limbs in 100% of the mice in saline-treated control. Abolition of this response by compounds was taken as the criterion of their anticonvulsant activity and expressed as percentage protection.

RESULTS AND DISCUSSION

The compounds had high LD_{50} values, *e.g.*, > 1000 mg/kg for I, II, V and VII–XI. Compounds III and VI had an LD_{50} of 1000 mg/kg and for IV it was 681 mg/kg. At 1/5th of the LD_{50} compounds did not produce any significant effect on the gross behaviour. Compound II was 40% active against metrazole-induced seizures while the rest of them were devoid of any activity against metrazole or electroshock induced seizures.

The results of pharmacological studies suggest that an aminomethyl group was desirable at position-12 in 11H-dibenzo[b,g]([1,3,6]triazonines for activity and the substitution of a chloro, amido or dialkyl amino group resulted in a loss of activity.

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